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Skeletal changes after restoration of the euparathyroid state in patients with hypoparathyroidism and primary hyperparathyroidism

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Abstract

Restoration of the euparathyroid state is associated with improvement of bone dynamics both in hypoparathyroidism and primary hyperparathyroidism. To date, no study has directly compared these two groups following correction of parathyroid hormone excess or deficiency. The study was designed to investigate changes in bone mineral density and trabecular bone score with restoration of the euparathyroid state by parathyroidectomy in primary hyperparathyroidism or recombinant parathyroid hormone [rhPTH(1-84)] replacement in hypoparathyroidism. This was a 2-year prospective intervention study in which we evaluated areal bone mineral density by DXA and trabecular bone score in 52 hypoparathyroid patients on rhPTH (1-84) replacement and 27 patients with primary hyperparathyroidism who underwent parathyroidectomy. We evaluated changes in areal bone mineral density by DXA and trabecular bone score at baseline, 6, 12, 18, and 24 months. After parathyroidectomy, areal bone mineral density increased from baseline at the lumbar spine and total hip at 6 months and at the femoral neck at 12 months, while there were no changes at the distal 1/3 radius. Treatment with rhPTH(1-84) was associated with significant increases in lumbar spine and decreases in distal 1/3 radius areal bone mineral density by 18 months in hypoparathyroid patients. At this time point, hypoparathyroid subjects demonstrated a significant increase in trabecular bone score from baseline, while there were no significant changes in trabecular bone score following parathyroidectomy. Bone mineral density increases both with administration of parathyroid hormone in a state of parathyroid hormone deficiency or removal of parathyroid hormone in a state of parathyroid hormone excess. However, only hypoparathyroid patients on rhPTH (1-84) appeared to have improvements in micro-architectural pattern as assessed by trabecular bone score.

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Conflict of interest DH is co-owner of the TBS patent and has corresponding ownership shares and interest in Medimaps group. All the other authors have nothing to disclose.

Keywords

Bone mineral density; Trabecular bone score; Hypoparathyroidism; Primary hyperparathyroidism; Parathyroidectomy

Introduction

Parathyroid hormone (PTH) is a key regulator of calcium metabolism and bone homeostasis [1]. Primary hyperparathyroidism (PHPT), a state of PTH excess, and hypoparathyroidism, a state of PTH deficiency, illustrate the two extremes of PTH effects on the skeleton. These two clinical phenotypes result in contrasting skeletal disorders. In PHPT, skeletal remodeling is typically excessive while in hypoparathyroidism, remodeling dynamics are markedly reduced [2–7].

The actions of PTH have classically been considered to be preferentially catabolic at cortical sites with relative sparing of trabecular sites. These observations are consistently demonstrated by areal bone mineral density (aBMD) measurements by DXA [1–3]. Despite these consistent aBMD findings by DXA, fracture risk is increased in PHPT at both trabecular (vertebral) and cortical (non-vertebral) sites [8–11]. This inconsistency is at least partially accounted for using newer imaging modalities, such as high-resolution peripheral quantitative computed tomography and Trabecular Bone Score (TBS) [12–16]. These techniques demonstrate that both cortical and trabecular skeletal compartments are adversely affected in postmenopausal women with PHPT [15, 16] better accounting for the increase in fracture risk observed in PHPT.

Longitudinal, randomized clinical trial data demonstrate increases in lumbar spine and femoral neck aBMD as early as 1 year after successful parathyroidectomy, while data from observational studies demonstrate that postoperative gains in aBMD are sustained for as long as 15-years at lumbar spine, hip and distal radius sites [17–19]. Micro-structural data also confirm the beneficial skeletal effects of parathyroidectomy [20].

In hypoparathyroidism, marked suppression of bone formation and resorption [4, 5] is associated with lower mineralizing surface, greater trabecular volume and width, and lower cortical porosity in comparison to age- and sex-matched euparathyroid subjects [5, 6]. Areal trabecular and cortical BMD are normal or above average values in hypoparathyroid patients. Data on fracture risk are inconclusive [5, 21, 22]. Treatment with human recombinant [rhPTH (1-84)] improves both skeletal compartments of bone with early restoration of bone dynamics to normal [23]. By DXA, bone mineral density increases at the lumbar spine with a modest but transient decline at the 1/3 radius site over a 4-year treatment period [24].

Only two studies have focused on comparative structural skeletal patterns associated with PTH excess and deficiency [25, 26]. Chen et al. reported that areal lumbar and radial BMD were higher in women with hypoparathyroidism as compared to hyperparathyroid women [26]. Volumetric BMD was also assessed by peripheral quantitative computed tomography

(pQCT) and found to be significantly higher in hypoparathyroid than hyperparathyroid patients [26].

To date, no study has investigated the changes in bone mineral density and TBS with restoration of the euparathyroid state by parathyroidectomy in PHPT, or rhPTH(1-84) replacement in hypoparathyroidism. This longitudinal study reports the findings of a study designed to address this issue.

Materials and methods

Subjects

We studied 52 hypoparathyroid patients and 27 patients with PHPT. Patients were recruited from the Metabolic Bone Diseases Unit of Columbia University Medical Center (CUMC) and from the Hypoparathyroidism Association.

The diagnosis of hypoparathyroidism was established historically by the presence of serum calcium and PTH levels below the lower limits of normal. The diagnosis of chronic hypoparathyroidism was defined as one year of persistently low calcium and PTH in association with requirement for calcium and/or active vitamin D supplementation. Patients with post-surgical hypoparathyroidism ($n = 32$), autoimmune-based disease or idiopathic hypoparathyroidism ($n = 19$) and one patient with the Di George syndrome were included. They were excluded from enrollment if they previously used PTH (1-34) or PTH (1-84). Hypoparathyroid subjects were treated with rhPTH (1-84) (NPS Pharmaceuticals, Bedminster, NJ) for up to 2 years. The earliest subjects enrolled were initially treated with a starting dose of 100 μg every other day [27]. Study physicians titrated calcium and vitamin D supplementation and PTH dose to 25, 50, and 75 μg daily based on biochemical parameters [28]. The 52 subjects who completed 2-years of treatment are included in this analysis.

PHPT was defined by the presence of simultaneously elevated serum calcium and elevated or inappropriately normal serum PTH levels. Among our 27 PHPT subjects, one was normocalcemic. Patients were referred for parathyroidectomy on the basis of the recommendations for surgery from the Third International Workshop on Asymptomatic PHPT [29]. Exclusion criteria included: bisphosphonate or glucocorticoid use within the past 2 years, recent pregnancy or breastfeeding (within past 6 months), a history of Cushing syndrome, uncontrolled thyroid disease, malabsorption syndrome, significant liver disease, creatinine clearance < 30 ml/min, chronic disorders of mineral metabolism such as Paget's disease, and osteogenesis imperfecta. We also excluded patients who were on anti-resorptive therapy for a minimum of 6 months duration within the two years of observation. The clinical diagnosis of PHPT was confirmed by histological documentation of parathyroid adenoma (70 %) or parathyroid hyperplasia (30 %) after surgery. Among PHPT patients, 27 subjects have reached the 6-month time point, 26 the 12-month, 20 the 18-month, and 13 the 24-month point.

Both men and women were enrolled. Postmenopausal status was defined as having no menstrual period for more than 1 year in both groups. The study was approved by the institutional review board of CUMC, and all subjects gave written informed consent.

Biochemical analysis

Serum total calcium (normal, 8.4–10.2 mg/dL) and albumin were measured using standard methods (Quest Diagnostics, Madison, New Jersey), and calcium values were corrected for albumin concentration <4 g/dL. Intact PTH (normal, 14–66 pg/mL) was measured by immunoradiometric assay (Scantibodies Laboratory, Santee, California) in the Bone Marker Laboratory at CUMC.

Bone mineral density (BMD)

Areal BMD by dual x-ray absorptiometry (Hologic, Waltham, MA) was measured at the lumbar spine (L1–L4), total hip, femoral neck, and non-dominant distal one-third radius. Measurements were performed at baseline and at months 6, 12, 18, and 24. Short-term in vivo precision error (root-mean-square SD) was 0.026 g/cm² for L1–L4 (1.1 %), 0.041 g/cm² for the femoral neck (2.4 %), and 0.033 g/cm² (1.8 %) for the forearm. Bone mineral density was expressed in grams per square centimeter and in T-score units.

Trabecular bone score (TBS)

Lumbar spine TBS measurement was performed blinded from Clinical outcomes, in the Bone Disease Unit at the University of Lausanne (Lausanne, Switzerland), using de-identified lumbar spine DXA files from scans obtained at CUMC. The TBS iNsight software (version 2.1; Medimaps group, Geneva, Switzerland) was used. TBS was evaluated by determining the variogram of the trabecular bone projected image, calculated as the sum of the squared gray-level differences between pixels at a specific distance and angle. TBS was then calculated as the slope of the log-log transform of this variogram [13]. A high TBS reflects strong, fracture-resistant microarchitecture; whereas a low TBS reflects weak, fracture-prone microarchitecture [13]. The added value of the TBS to bone mineral densitometry in fracture risk assessment has been documented in cross-sectional, prospective and longitudinal studies and endorsed by medical societies such as ESCEO [30] and ISCD (www.iscd.org). TBS was calculated as the mean value of the individual measurements for L1–L4 which represents lumbar spine TBS. For longitudinal comparison, we calculated TBS as the average TBS of all vertebral bodies included for analysis. If any vertebra was excluded, all subsequent TBS calculations were adjusted to ensure that identical vertebral bodies were analyzed.

The calibration of the DXA instrument at CUMC was performed using a TBS-specific phantom (Medimaps). TBS intervention thresholds have been evaluated based on a tertile approach [30] using a recent meta-analysis of 14 prospective population-based cohorts (excluding Manitoba cohort) comprising 17,809 men and women (59 % women). That is to say two thresholds have been determined corresponding to 1.23 and 1.31 respectively considering the region of interest including the four lumbar vertebrae (L1 to L4) and thus independently of the gender.

A sub-analysis has been performed showing that no gender effect exists. To establish a relative scale of abnormality, we will define the subjects above 1.31 as being at low risk of fracture (i.e. normal pattern), between 1.31 and 1.23 at intermediate risk (i.e., partially degraded micro-architectural pattern) and below 1.23 at high risk of fracture (i.e., degraded pattern).

Statistical analysis

Baseline characteristics of subjects with hypoparathyroidism and with PHPT were examined and compared. Between-group differences in means for continuous variables were assessed with two-sample *t*-test. Differences in categorical variables were assessed with Chi-Square test. Fisher's Exact Test was applied instead when Chi-square test is not valid. Linear mixed models for repeated measures were applied to assess the parameter change at different time points, with time, group, and time-group interaction term as the fixed effect, adjusted for baseline parameter values. General change trend over time was examined for each group separately using linear mixed models with time as fixed effect, adjusted for the same covariates. Either compound symmetry or autoregressive covariance structure was applied in model fitting as appropriate. The least square means of percent change from baseline values of L1-L4-BMD, femoral neck BMD, total hip BMD, and one-third radius BMD, and TBS in each group were examined, and then between-group differences comparison was assessed with mixed models. *P*-values < 0.05 were used to establish significance. Statistical analysis was performed using SAS (version 9.4; SAS Institute, Inc, Cary, North Carolina).

Results

At baseline, patients with hypoparathyroidism were younger, had longer duration of disease and significantly lower calcium and PTH values compared with patients with PHPT (Table 1). The two groups did not differ in body mass index (BMI), ethnic composition or in gender distribution.

Areal bone mineral density was normal at the lumbar spine in both hypoparathyroid and PHPT patients, but it was lower in PHPT compared to hypoparathyroid subjects (Table 1). At the femoral neck, total hip and one-third radius sites, patients with PHPT had T-score values in the osteopenic range and had significantly lower aBMD than their hypoparathyroid counterparts in whom aBMD was normal at all sites. TBS was normal in hypoparathyroid patients, and significantly higher than in PHPT patients, in whom microarchitecture fit into the classification of "partially degraded" despite their normal spine aBMD.

After parathyroidectomy, aBMD increased promptly from baseline values at the lumbar spine, femoral neck and total hip regions. After adjustment for baseline aBMD, these increases were significant as early as 6 months at the lumbar spine and total hip and by 12 months at the femoral neck. The improvement over baseline continued to increase through 24 months at lumbar spine and total hip sites, and through 18 months for the femoral neck site ($p < 0.01$) (Fig. 1). The 1/3 radius site did not show any changes through the 2-year post-operative period, consistent with our earlier observations that this site does not begin to show improvements over this rather short period of time [18]. TBS of the lumbar spine did not change after parathyroidectomy (Fig. 2).

These findings contrast with those of subjects with hypoparathyroidism followed for this same period of time after administration of rhPTH (1-84). At the lumbar spine, aBMD increased in both groups, although the change was slower in hypoparathyroid patients, achieving significance relative to baseline ($p < 0.001$) a full year after significance was achieved after parathyroidectomy in PHPT (18 vs. 6 months; Fig. 1). Mean percentage change between groups did not differ. Also different from the postoperative changes at the femoral neck and total hip in PHPT, rhPTH(1-84) administration was not associated with any changes over this two-year period. Distal 1/3 radius aBMD was unchanged after parathyroidectomy in PHPT, while rhPTH (1-84) treatment was associated with significant reductions by 18 months (Fig. 1). The small increase in distal 1/3 radial aBMD at 12 months was transient.

With regard to TBS, hypoparathyroid subjects demonstrated by 18 months a significant increase from baseline ($p < 0.02$), in contrast to the lack of change among the subjects with PHPT after parathyroidectomy (Fig. 2). There were no significant correlations between the changes in TBS and aBMD confirming that both parameters are reflecting different bone entities.

Mean aBMD and TBS values at 24 months for both groups are reported in Table 2. Hypoparathyroid patients receiving rhPTH(1-84) continued to have significantly higher aBMD (absolute and by T-Score) at all sites compared with PHPT patients. After parathyroidectomy, T-scores normalized at the total hip but remained osteopenic at the femoral neck and one-third radius. After two years of rhPTH(1-84) replacement therapy, hypoparathyroid patients continued to have normal aBMD values at all sites. TBS values remained significantly higher among the subjects with hypoparathyroidism.

Discussion

This study presents, for the first time, comparative data on structural changes of the skeleton during improvement of parathyroid function in patients with baseline PTH deficiency or excess. Consistent with our previous work, lumbar spine aBMD appears to benefit from both correction of PTH excess in PHPT and from PTH replacement in hypoparathyroidism [17–19, 24]. The difference in kinetics of change at the lumbar spine, with the hyperparathyroid subjects realizing faster gains is likely to reflect the baseline higher level of bone remodeling in PHPT. This higher level of skeletal metabolic activity may serve as a “primer” allowing faster gains than are seen in a very low turnover state such as hypoparathyroidism, in which time is required before bone accrual is apparent. A similar lag has been reported with regard to the use of PTH(1-84) after bisphosphonate therapy [31]. Since the lumbar spine contains primarily trabecular bone, one can therefore speculate that restoration of the euparathyroid state improves this skeletal compartment in both disease states.

Also consistent with previous reports, we observed a sustained and gradual increase in femoral neck aBMD in PHPT patients after surgery, while there were no notable changes in subjects with hypoparathyroidism at this site [17–19, 24]. This again may reflect the differing states of bone turnover (increased in PHPT vs. reduced in hypoparathyroidism) at time of initiation of treatment.

The decline in aBMD at the distal 1/3 radius in hypoparathyroid patients treated with rhPTH(1-84) is due to the effects of PTH on cortical bone, and has been seen repeatedly in states of excess of PTH (PHPT) and in the therapeutic use of teriparatide for osteoporosis [2, 32]. However, the reduction in aBMD at this site has not been associated with an increase in fracture risk. In fact, with the use of teriparatide in osteoporosis, the incidence of non-vertebral fractures, representing primarily effects at the cortical skeleton, is reduced [32]. It is therefore likely, although unknown, that the same response will be seen in the context of rhPTH(1-84) therapy of hypoparathyroidism as in the treatment of osteoporosis.

No significant gain in aBMD at the 1/3 radius was observed in PHPT patients after surgery, a finding that is consistent with previous reports [17–19] showing little or no changes in cortical aBMD in the short term. Changes after parathyroidectomy at this site require a substantially longer follow up period [17–19].

The post-operative increase in aBMD results from the change from a catabolic state due to chronically elevated PTH levels to more balanced physiological dynamics from the remaining normal parathyroid glands [19, 33]. The early improvement in aBMD is associated with mineralization of unmineralized bone matrix in the remodeling space, in which the amount is significantly and typically increased in PHPT [19, 33, 34]. The slower increase in lumbar spine aBMD in the hypoparathyroid group is consistent with histomorphometric studies which identified a peak in bone-formation rate only one year after rhPTH(1-84) is initiated [23]. Prolonged stimulation by rhPTH (1-84) is likely necessary in a low turnover, unprimed skeleton [23]. In short, the increase in aBMD after parathyroidectomy is best explained by a reduction in the remodeling space, while the increase in BMD after rhPTH (1–84) is best explained by an osteoanabolic effect of PTH itself. Taken together, these mechanisms explain the significant gain in spine aBMD in both groups, and account for the different timing profile we observed in our study.

The analysis by TBS offers further insight into trabecular micro-architectural pattern in these two cohorts. Interestingly, while baseline lumbar spine T-score values were normal in both groups, TBS was normal only in hypoparathyroid subjects, while in PHPT TBS values demonstrated partially degraded microarchitecture, in agreement with prior studies [13, 15, 20, 35]. Muschitz et al. demonstrated that TBS was strongly correlated with transiliac bone biopsy micro-architectural parameters in more than 123 patients (both men and women) [13]. They concluded that TBS is a practical, non-invasive, surrogate technique for the assessment of cancellous bone microarchitecture and should be implemented as an additional tool for the determination of trabecular bone properties [13]. If TBS is a surrogate marker for trabecular microstructure, relative preservation in hypoparathyroidism might be explained, at least in part, by the low turnover state characteristic of this disease. Alternatively, there might be other aspects of skeletal micro-structure that are not captured by TBS technology contributing to the differences between these two disorders of parathyroid function.

In hypoparathyroid patients, the improvement in TBS occurred in parallel with aBMD gains at the lumbar spine. These data are consistent with our previous histomorphometric findings, further demonstrating that rhPTH(1-84) improves microstructural properties of the newly

formed bone in hypoparathyroidism and with data from the same population of hypoparathyroid patients showing that TBS continues to increase for a mean follow-up time of 69 ± 16 months [36].

The increase in lumbar spine BMD has been described for up to 4 years in hypoparathyroid patients during replacement therapy [24]. Further data including a longer follow up period will clarify whether the beneficial effects on trabecular microarchitecture are maintained. In PHPT, cancellous architecture evaluated by TBS and HR-pQCT has shown improvements after parathyroidectomy [20, 37, 38]. We did not find such an increase in TBS, possibly because of the small numbers of study subjects observed for the full two-year period. An alternative hypothesis to account for these observations is that the faster gain in trabecular aBMD in patients after surgery does not rapidly translate into a microarchitectural benefit. Data from a longer period of observation after parathyroidectomy will help to distinguish between these two explanations.

Our study has some limitations. Because of the different epidemiology of the two diseases, the cohorts of patients had differences in baseline characteristics. Additionally, we did not have available a control group to overcome issues related to the different clinical profile. The limited number of PHPT patients in the second year of the study may have affected the statistical power of some of the analyses. Finally, the correlation of our data with bone markers data could have improved our understanding of mechanisms associated with metabolic changes in the bone in conditions where the excessive stimulus to resorption is removed and the stimulus to bone remodeling is re-introduced.

In conclusion, this is the first study demonstrating both areal BMD and TBS responses to the restoration of the euparathyroid state in hypoparathyroidism and PHPT. It provides heretofore unavailable comparative information between the administration of PTH in a state of PTH deficiency or removal of PTH in a state of PTH excess. Although skeletal properties are affected in a different manner in the two disorders, beneficial results are seen in both conditions.

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Fig. 1.

Percentage change from baseline in aBMD by DXA of the lumbar spine **a**, femoral neck **b**, total hip **c** and one-third radius **d** in patients with hypoparathyroidism (circles) during treatment with PTH(1-84) and in PHPT patients (triangles) after parathyroidectomy. Data are expressed as mean values $\pm$ SE. *Significantly different ($p < 0.05$) from baseline

Fig. 2. Percentage change in Trabecular Bone Score (TBS) from baseline in patients with hypoparathyroidism (circles) during treatment with PTH(1-84) and in PHPT patients (triangles) after parathyroidectomy. Data are expressed as mean values $\pm$ SE. *Significantly different ($p < 0.05$) from baseline

Table 1Baseline characteristics (mean $\pm$ SD) of subjects with hypoparathyroidism and with PHPT

Characteristics	Hypoparathyroidism (<i>n</i> = 52)	PHPT (<i>n</i> = 27)	<i>p</i> -value ^a
Age, y	47.6 $\pm$ 12.5	63.5 $\pm$ 12.4	<0.0001
Height, cm	164.6 $\pm$ 7.9	167.2 $\pm$ 9.6	NS
Weight, kg	74 $\pm$ 17.6	76.8 $\pm$ 19.2	NS
BMI, kg/m ²	27.3 $\pm$ 6.5	28 $\pm$ 5.6	NS
Ethnicity, n (%)			
Caucasian	50 (96 %)	26 (96.3 %)	NS
Hispanic	2 (4 %)	0	
Black	0	1 (3.7 %)	
Gender, n (%)			
Women	41 (79 %)	20 (71 %)	NS
Men	11 (21 %)	8 (29 %)	
Premenopausal women	22 (54 %)	1 (5 %)	<0.001
Postmenopausal women	19 (46 %)	19 (95 %)	
Years since diagnosis ^b	14.7 $\pm$ 14.2	7.4 $\pm$ 9.3	<0.01
Serum total calcium, mg/dL	8.6 $\pm$ 1	10.9 $\pm$ 0.6	<0.0001
PTH, pg/mL	4 $\pm$ 3	115 $\pm$ 59	<0.0001
L1-L4 aBMD, g/cm ²	1.190 $\pm$ 0.221	0.974 $\pm$ 0.187	<0.0001
T-score	1.2 $\pm$ 2	-0.8 $\pm$ 1.7	
Femoral Neck aBMD, g/cm ²	0.938 $\pm$ 0.187	0.697 $\pm$ 0.128	<0.0001
T-score	0.6 $\pm$ 1.6	-1.5 $\pm$ 1.0	
Total hip aBMD, g/cm ²	1.060 $\pm$ 0.181	0.833 $\pm$ 0.152	<0.0001
T-score	0.8 $\pm$ 1.3	-1.1 $\pm$ 1.1	
1/3 Radius aBMD, g/cm ²	0.733 $\pm$ 0.067	0.642 $\pm$ 0.109	<0.0001
T-score	0.2 $\pm$ 0.9	-1.5 $\pm$ 1.8	
TBS	1.44 $\pm$ 0.12	1.28 $\pm$ 0.13	<0.0001

^a Assessed with two-sample *t*-test (continuous variables), Chi-Square test and Fisher's Exact Test when Chi-square test is not valid (categorical variables)

^b Years since diagnosis and prior to surgery in PHPT patients

Table 2Skeletal parameters (mean $\pm$ SD) in subjects with hypoparathyroidism and with PHPT at 24 months

Parameter	Hypoparathyroidism (<i>n</i> = 52)	PHPT (<i>n</i> = 13)	<i>p</i> -value ^a
L1-L4 aBMD (g/cm ²)	1.228 $\pm$ 0.229	1 $\pm$ 0.162	<0.001
T-score	1.6 $\pm$ 2.1	−0.5 $\pm$ 1.5	
Femoral Neck aBMD (g/cm ²)	0.937 $\pm$ 0.183	0.713 $\pm$ 0.139	<0.0001
T-score	0.6 $\pm$ 1.6	−1.4 $\pm$ 1.1	
Total hip aBMD (g/cm ²)	1.058 $\pm$ 0.178	0.872 $\pm$ 0.175	<0.001
T-score	0.7 $\pm$ 1.3	−0.8 $\pm$ 1.2	
One-third Radius aBMD (g/cm ²)	0.717 $\pm$ 0.074	0.641 $\pm$ 0.12	<0.0001
T-score	−0.01 $\pm$ 1	−1.6 $\pm$ 1.4	
TBS	1.45 $\pm$ 0.11	1.30 $\pm$ 0.13	<0.0001

^a Assessed with two-sample *t*-test for aBMD and T-score